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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/855,886	05/15/2001	Barry Coller	A31386-A	1518

21003 7590 11/09/2004

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/855,886	COLLER ET AL	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-11 and 15-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-11 and 15-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ ~~Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)~~ Paper No(s)/Mail Date *8/30/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ ~~Notice of Informal Patent Application (PTO-152)~~
6) ☐ Other: _____.

DETAILED ACTION

1. The request filed on 8/30/04 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/855,886 is acceptable and a RCE has been established. Claims 1-3, 5-11, 15-17 are pending and are currently under prosecution. An action on the RCE follows.

2. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

3. Claims 10-11 have been amended.

4. Claims 1-3, 5-11, 15-17 are under examination.

Response to Arguments

5. The rejection of claims 1-3, 5-11, 15-17 under 35 U.S.C. 103(a) as being unpatentable over Max et al (Int. J. Cancer 71:320-324, 1997) in view of Taylor et al (Blood 89:4078-4084, 1997) and Mohle et al (PNAS 94:663-668, 1997) and Charo et al (J. Biol. Chem. 262:9935-38, 1987) as evidenced by Coller et al (Haemostasis 26:285-293, 1996) is maintained.

The response filed 8/30/04 has been carefully considered but is deemed not to be persuasive. The response states that Applicants request the Examiner to reconsider the basis for the rejection and to afford Applicants the opportunity to restate and clarify their position regarding Max. The response states that as background Max states that αVβ3 might be a useful therapeutic target for cancer characterized by pathological

angiogenesis and then states until now the use of a complex-specific antibody against the most interesting target, αVβ3, has been limited and applicants interpret these statements to mean that while LM609 appeared to inhibit angiogenesis, previous attempts did not address whether αVβ3 would support the relevance of this complex to LM609's purported anti-angiogenic effect and as indicated in Max there are no clues regarding the function of αVβ3 in normal tissue (see page 6-7 of response). In addition the response states that reading Max one would understand that while the up-regulation of αVβ3 in tumor vasculature is consistent with a functional role for αVβ3 in tumor angiogenesis, the presence of αVβ3 on normal cells is not and because of this ambiguity it would not be obvious that an antibody that is an antagonist of αVβ3 and GpIIb/IIIa, such as 7E3, would inhibit angiogenesis (see page 7 of response).

In response to this argument, when reading Max et al as a whole as stated in the response one would readily understand the role of αVβ3 in angiogenesis specifically tumors and other diseases associated with angiogenesis such as inflammation. In addition, although Max does state that there are no clues to the function of αVβ3 expression in normal tissue, Max et al goes on to state that "it is possible that αVβ3 expression on the normal vasculature does not serve any angiogenic function at all, and endothelial cells in normal tissue do not depend on αVβ3 ligation for survival." (see page 324 right column of Max et al) and "Besides the differences in the number of αVβ3-expressing vessels in normal and neoplastic tissue, there also seems to be a stronger staining in tumors (see page 323, left column). Thus, there appears to be no ambiguity regarding the role of αVβ3 in angiogenesis associated with disease such as

tumor and when reading Max et al one skill in the art would conclude that inhibitors of αVβ3 would inhibit angiogenesis and could be used for inhibiting angiogenesis.

The response further states that to further support their arguments regarding the ambiguity of the association between αVβ3 and angiogenesis, applicants have cited art from the laboratory of Dr. Hynes (see pages 8-9 of response). The first is Taverna et al Proc. Am. Assoc. Cancer Res 38:290-291, 1997 which is cited for teaching alpha5 as a tumor suppressor gene and the response states that this reports conflicting data regarding whether or not alphaV has anti-tumor effect. In response to this argument, the reference is directed to alpha5 not alphaV, there is no mention of alphaV in the reference, therefor, it has nothing to add to the argument.

The next reference is Hynes and Bader, Thrombosis and Haemostasis 78:83-87, 1997 which is stated to teach mutations in alphaV still led to extensive development of heart and vasculature and it is possible that different forms of angiogenesis exist, which differ in their requirement for alphaV. In response to this argument, the reference is directed to normal development not tumor or angiogenesis in a diseased state. The reference adds support to the teachings of Max et al in that alphaV in normal vasculature does not serve any angiogenic function.

The third reference is Taverna et al PNAS 101:763-768, 2004. This reference is stated to teach alphaV integrins could act as negative regulators of angiogenesis and cites references in the paper. In response to this argument all of the references as well as the Taverna et al reference were all published after the filing date of the instant

application (which is 5/2001) and as such one skill in the art would not have looked to these references since they were not available at the time of the claimed invention.

The response then states that the Examiner is directed to the art of Trikha et al Cancer Research 62:2824-2833, 2002 that demonstrates the success of the claimed invention and such results would not have been expected based on the combination of references cited (see pages 9-10 of response). In response to this argument, while the art of Trikha et al may demonstrate the success of the claimed method, the reference was published after the filing date of the instant application and adds nothing to the argument, except that the claimed invention was produced by another group post filing.

The response further states that the Examiners attention is drawn to several articles that are supporting evidence for patentability of claims 10, 11, 15-17 (see page 10-11 of response). In response to this argument, it is unclear what the references are to provide except for enablement and there is no enablement rejection to address.

Thus, it would have been obvious to inhibit angiogenesis with an antagonist to both αVβ3and GPIIb/IIIa because both are implicated in angiogenesis (which plays a key role in inflammation and cancer) by overexpression of VEGF by activated platelets wherein platelet activation is GPIIb/IIIa dependent and αVβ3 is implicated in tumors and treatment of tumors can be performed with αVβ3 antagonist. In addition, as taught by Max et al tumor induced angiogenesis may be initiated by release of angiogenic factors from tumor and inflammatory cells and this appears to indicate that angiogenesis might be enhanced by inflammatory cells (see page 323, right column). This indicates that one would want to inhibit angiogenesis as well as inflammation because both are

implied to be associated. Therefore, it would have been obvious to use an antagonist of both αVβ3 and GPIIb/IIIa and use the 7E3 antibody which obviously have the claimed properties of the antagonist.

Conclusion

6. No claim is allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (571) 272-0832. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffery Siew, can be reached on (571) 272-0787.

8. Papers related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

571-272-0832

LARRY R. HELMS, PH.D
PRIMARY EXAMINER